Linkage analysis in families with aortic aneurysm

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Ethical review	Not approved
Status	Will not start
Health condition type	Chromosomal abnormalities, gene alterations and gene variants
Study type	Observational invasive

Summary

ID

NL-OMON33364

Source
ToetsingOnline

Brief title
Linkage analysis in families with AA

Condition

- Chromosomal abnormalities, gene alterations and gene variants
- Aneurysms and artery dissections

Synonym
aortic aneurysm, dilatation of the aorta

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Stichting Nuts Ohra,stichting Nuts Ohra;Nederlandse Hartstichting

Intervention

Keyword: aortic aneurysm, linkage analysis

Outcome measures

Primary outcome

genetic defect

Secondary outcome

nvt

Study description

Background summary

Aneurysms and dissections are the major diseases affecting the aorta. They lead to substantial morbidity and mortality in case of rupture. In general AA is considered to be a complex disorder, in which both environmental and genetic factors contribute to its development. But there are families in which the condition follows a mendellian inherited pattern. Identification of the genetic defect in these families will greatly contribute to the understanding of the pathology of AA formation. In addition, this will be of great value for the family members. With minimal strain, they can then be screened for having the genetic predisposition. Subsequently, they can either be reassured, or be admitted in an inndividualized surveillance program (see burden and risks).

Study objective

The aim of the study described in this protocol is the identification of genes involved in aortic aneurysm development. This will be achieved by characterization of large AA families, including pedigree investigations, diagnostic measurements (echocardiograms and abdominal ultrasounds), linkage analysis and sequencing of candidate genes.

Study design

Patients
AA patients that visit their specialist (vascular surgeon or cardiologist) will be asked whether an AA runs in their family. This a general question, because of the inherited nature of AA. If the family has at least 3 known cases of AA, the patient is informed about the study and receives patient information from

the specialist. He-she is asked if the specialist can provide contact information to the researcher. If the indexpatient agrees, the researcher will invite the patient for a consult at the Medical Genetics department in the UMC Utrecht. The study will be explained in detail, and informed consent is obtained. With help of the patient, an initial pedigree will be constructed. Subsequently, the indexpatient is asked to inform his-her family members about the study, and to give them the patient information. If they are interested in participating, they can contact the researcher. They will be invited for a consult at the Medical Genetics department in the UMC Utrecht. The study will be explained in detail, and informed consent is obtained. Family members of whom it is unknown whether they have an AA will be invited for an ultrasound examination or for an echocardiogram in the hospital from the indexpatient (for now the Antonius hospital and the Erasmums MC respectively). With all the obtained information, the pedigree will be finalized.

Methods
Once the pedigree is finalized, blood will be obtained from all family members whom have given informed consent and DNA will be isolated. We will use Illumina*s SNP-based linkage panel V, which includes 6056 SNPs, to conduct linkage analysis using an *affected-only* approach. Both parametric and non-parametric analysis will be carried out with the Merlin and Simwalk programs. Haplotypes of LOD scores>2 will be fitted to the full family pedigree using Cyrillic to check for the consistency of shared haplotypes of affected family members. Subsequently, the boundaries of the locus with the best solution will be determined. We will determine which genes in the locus are good candidate genes based on the current pathophysiological knowledge, and these will be sequenced. If possible, all genes in the locus will be sequenced.

Study burden and risks

Burden and risks are minimal (1x blood withdrawal, diagnostic test).
Identification of the causal gene in AA families will be of great value for the family members. With minimal strain, they can then be screened for having the genetic predisposition. Subsequently, they can either be reassured, or be admitted in a specialized surveillance program. This program will be carefully composed by the specialist, based on the age of the patient, and the family history of AAs (age of onset, age of rupture). For example: patients of 40 years and older with the genetic predisposition will be invited for a yearly ultrasound examination. If the diameter of the aorta does not increase within 5 years, together, the specialist and patient can decide to extend the intervals between the examinations. If the aorta enlarges, shorter intervals between the examinations may be required. If surgery is required, based on diameter or on velocity of growth, proper action can be undertaken.
The knowledge of having the genetic predisposition, or of having an AA, will have psychological and medical consequences. This will be emphasized during the consult with the researcher, prior to giving informed consent (in which the patient has to indicate whether he/she wants to know if he/she has the genetic

predisposition). Furthermore, during ultrasound examination, other disorders can be discovered. The knowledge of this may also have psychological and medical consequences. The patient is informed about this, and asked if he/she wants to know about these potential other disorders. If not, the patient can not be included in the study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

familymembers from families with at least 3 known cases of aortic aneurysms

Exclusion criteria

Less than 3 aortic aneurysms in family

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	44
Type:	Anticipated

Ethics review

Not approved

Date:	27-10-2009
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL27456.041.09